(i) an immunoadsorption on an affinity column prepared with the pre-immune Ig of the animal which has been used to produce the anti-VEGF IgG, to eliminate the anti-allotypic or isotypic antibodies,

(ii) an immunoadsorption on an affinity column prepared with the anti-VEGF IgG, to purify the anti-idiotypes.

R E M A R K S

Claims 25-30 and 32-35 are pending with claims 25 and 26 being independent.

The Official Action objected to the drawings for not having a legend in Figure 5 of the drawings. We herewith propose to amend this drawing by the accompanying Request for Permission to Make Drawing Corrections letter. Withdrawal of the drawing objection is therefore solicited.

The Official Action rejected claims 25-30 and 32-35 under §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. That rejection is respectfully traversed, for the following reasons.

The Official Action contended that the declaration by Jean Plouet teaches the production of polyclonal antiserum containing polyclonal antibodies would not result in the

claimed invention. The Official Action further contended that the declaration teaches that more key steps are required to produce and screen monoclonal antibodies that are being claimed. In response, however, applicants call to the Examiner's attention that the declaration actually states that both polyclonal and monoclonal antibodies comprise a significant number of antibodies that bind to flk-1 and/or flt-1. Each of the polyclonal and monoclonal antibodies produce antibodies that bind to flk-1 alone. The claims require that the antibody be a ligand of the human KDR receptor or the murine flk-1 receptor exclusively.

Claim 30 has been amended to teach a method of obtaining both monoclonal and polyclonal antibodies. The rabbit anti-VEGF Ig can be injected into a rabbit in order to produce polyclonal antibodies; mouse anti-VEGF Ig can be injected into a mouse in order to produce monoclonal antibodies. The specification discloses a method for producing both polyclonal and monoclonal antibodies on page 8, lines 5-13. The disclosure provides for a method to produce antibodies using the same species for anti-VEGF IgG retrieval as for antibody retrieval. A mouse is an animal and, when it produces antibodies, it produces monoclonal antibodies. Therefore, claim 30 is not new material.

The specification teaches the screening processes used to isolate the antibodies that bind exclusively to the flk-1 receptor. These screening processes described in the specification enable one skilled in the art to make and use

the invention. The specification teaches using polyclonal antibodies, but the teachings do not exclude using monoclonal antibodies.

These screening processes involve a radioreceptor assay which allows to discriminate between antibodies with flk-1 and flt-1 ligands. The radioreceptor assay is described in the specification on page 17: "Screening of the anti-idiotypic antibodies is carried out in accordance with the following sequence developed in the laboratory: ... The data are then analysed in accordance with the Scatchard plot (Scatchard, 1949) using the Munson program (Munson, 1980)."

The section named "RESULTS" on pages 21 to 22 of the specification refers to the Scatchard plot to get antibodies that specifically bind flk-1 alone. The specification, therefore, teaches how to make the claimed antibody with the flk-1 or KDR ligand, using the screening method described in the specification. The screening method [Scatchard method] enables any person skilled in the art to make and use the invention.

The Official Action also contended that the Fab fragments of claims 27 and 28 could not perform the claimed function of the antibodies. The Examiner understood through Plouet's declaration that the Fab fragments cannot exert the same functional activity as the antibodies, because they cannot induce "dimerization, internalization and cell proliferation." In response, applicants confirm that the ligands formed between the Fab fragments and the KDR or flk-1 indeed

prevent the proliferation of endothelial cells. However, the Fab fragment coupled with a toxin is used, consistent with preferred embodiments, to form ligands with the angiogenic cells with the KDR or flk-1 receptors to prevent cell proliferation and to kill the cells. The Fab fragments are, therefore, functionally equivalent to the antibodies for this aspect of the invention.

In light of the amendments and explanation discussed above, applicants believe that the present application is in condition for allowance and an early indication of the same is respectfully requested.

If the Examiner has any questions or requires clarification, the Examiner may contact the undersigned attorney so that this application may continue to be expeditiously advanced.

Attached hereto is a marked-up version of the changes made to claim 30 by the current amendment. The

attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

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"Version with markings to show changes made."

IN THE CLAIMS:

Claim 30 has been amended as follows:

30. (thrice amended) Anti-idiotypic antibody according to claim 25 produced by the following steps:

a) purified VEGF is injected into [a rabbit] an animal,

b) blood is withdrawn to recover purified Ig containing specific anti-VEGF IgG, and then in an optional stage the specific anti-VEGF IgG are purified from the purified Ig,

c) said purified Ig or said purified anti-VEGF IgG are injected into [the popliteal ganglions of a rabbit] an animal of the same origin as that used for injection of the VEGF,

d) blood is withdrawn to recover the total Ig, and then to subject the total Ig to two immunoadsorptions:

(i) an immunoadsorption on an affinity column prepared with the pre-immune Ig of the [rabbit] animal which has been used to produce the anti-VEGF IgG, to eliminate the anti-allotypic or isotypic antibodies,

(ii) an immunoadsorption on an affinity column prepared with the anti-VEGF IgG, to purify the anti-idiotypes.

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Figure 5